Tetrahedron 66 (2010) 6806–6813

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

The stereodivergent aziridination of allylic carbamates, amides and sulfonamides

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ARTICLE INFO

Article history:
Received 5 May 2010
Received in revised form 9 June 2010
Accepted 21 June 2010
Available online 25 June 2010

Keywords:
Aziridine
Allylic amine
Substrate-directed reaction
Stereodivergent

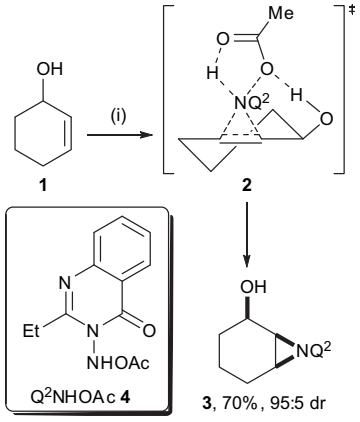
ABSTRACT

A stereodivergent protocol for the aziridination of a range of cyclic allylic amine derivatives has been developed. *syn*-Products can be obtained in >99:1 dr under H-bonded control and *anti*-products are obtained in >99:1 dr under steric control by judicious choice of the *N*-protecting groups.

1. Introduction

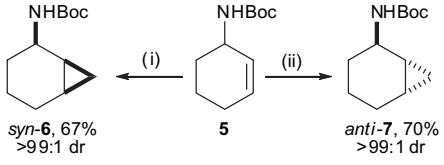
Aziridines are the nitrogen analogues of epoxides and are useful intermediates in organic synthesis. Several well-established methods for the synthesis of aziridines from olefins are known,[1] with 1,3-dipolar cycloaddition of azide followed by decomposition of the intermediate triazoles,[2] Michael addition of a nitrogen nucleophile followed by expulsion of a leaving group,[3] the addition of IN_3 or INCO followed by reductive or hydrolytic ring-closure,[4] and the direct addition of a nitrene species or equivalent[5,6] being amongst the most popular. However, there are relatively few examples of stereoselective substrate-directed aziridination reactions known.[7] Atkinson et al. have used this approach for the aziridination of both allylic and homoallylic alcohols.[8] For example, aziridination of 2-cyclohexen-1-ol **1** with C (2) - ethyl substituted 3-acetoxyaminoquinazolinone (Q^2NHOAc) **4** is reported to give *syn*-**3** in 95:5 dr and 70% isolated yield;[9] a H-bonded transition state **2** (analogous to that proposed by Bartlett for olefinic epoxidation)[10] is postulated to account for the high level of *syn* diastereoselectivity observed (Scheme 1).[11]

Within the area of stereoselective substrate-directed reactions O'Brien et al. have reported the stereoselective epoxidation of a range of *N*-protected 2-cyclohexen-1-ylamines.[12] Furthermore, we have recently reported the chemo- and diastereoselective epoxidation of allylic and homoallylic amines,[13a–c] and the cyclopropanation of allylic amines and carbamates.[13d–e] For example, the stereodivergent cyclopropanation of *tert*-butyl cyclohex-2-en-1-ylcarbamate **5** gave either *syn*-**6** upon treatment with



Scheme 1. Reagents and conditions: (i) Q^2NHOAc **4**, CH_2Cl_2, rt.

$Zn(CH_2I)_2$ (the Wittig–Furukawa reagent) or *anti*-**7** upon treatment with $F_3CCO_2ZnCH_2I$ (Shi's carbenoid) in good yield and >99:1 dr in both cases (Scheme 2).[13d]



Scheme 2. Reagents and conditions: (i) Et_2Zn, CH_2I_2, CH_2Cl_2, rt, 1 h; (ii) Et_2Zn, CH_2I_2, TFA, CH_2Cl_2, rt, 1 h.

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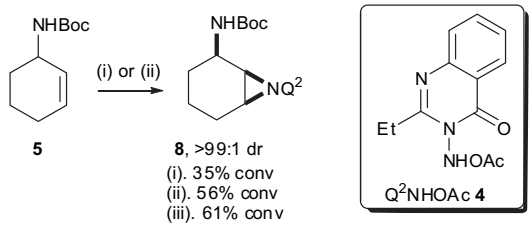
doi:10.1016/j.tet.2010.06.059

We considered that this methodology may be extended to encompass the stereoselective substrate-directed aziridination of allylic amine derivatives. A recent report by Kilic et al. concerning the diastereoselective aziridination of chiral acyclic allylic alcohols[14] has prompted us to publish our initial findings within this area, which are delineated herein.

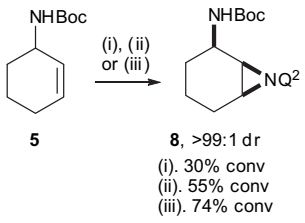
2. Results and discussion

Our initial studies focused on the aziridination of *N*-Boc protected allylic amine **5**[15] with 3-acetoxyaminoquinazolinone **4** (Q^2NHOAc).[9] A variety of reagents and conditions were screened in order to find an effective combination to promote the formation of aziridine **8** in good yield and with high diastereoselectivity.[16] Treatment of carbamate **5** with 2.0 equiv of 3-acetoxyaminoquinazolinone **4** at either −23 °C or 0 °C returned only starting material, whereas reaction at ambient temperature gave a single diastereoisomer of aziridine **8** in 35% conversion. In addition, it was found that the percentage conversion after stirring for 24 h at ambient temperature was approximately the same as that for stirring at 2.5 h at the same temperature. This result was consistent with reports that 3-acetoxyaminoquinazolinone **4** is known to be stable at −23 °C but not at ambient temperature.[6] In an attempt to improve the level of conversion, aziridination of carbamate **5** with 4.0 and 8.0 equiv of 3-acetoxyaminoquinazolinone **4** gave aziridine **8** in 56 and 61% conversion, respectively, and in >99:1 dr in each case (Scheme 3).[17] The relative *syn*-configuration within **8** was tentatively assigned by analogy to the H-bond directed aziridination of allylic alcohol **1**.



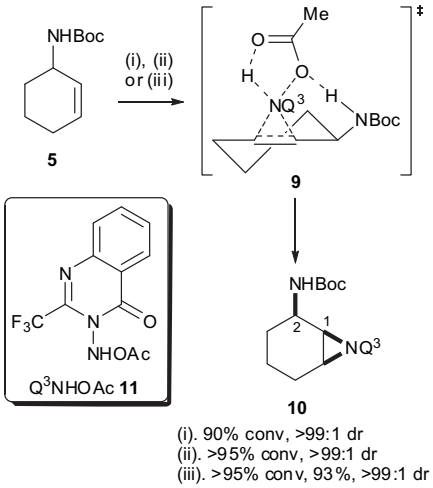
Scheme 3. Reagents and conditions: (i) Q^2NHOAc **4** (2.0 equiv), CH_2Cl_2, rt, 2.5 h; (ii) Q^2NHOAc **4** (4.0 equiv), CH_2Cl_2, rt, 2.5 h; (iii) Q^2NHOAc **4** (8.0 equiv), CH_2Cl_2, rt, 2.5 h.

It has previously been reported that the addition of hexamethyldisilazane (HMDS) to the reaction mixture gives improved yields for aziridination products as the rate of decomposition of 3-acetoxyaminoquinazolinone **4** is decreased.[18] Aziridination of carbamate **5** with 2.0 equiv of 3-acetoxyaminoquinazolinone **4** in the presence of 3.0 equiv of HMDS gave aziridine **8** in 30% conversion and >99:1 dr. To determine if the lifetime of 3-acetoxyaminoquinazolinone **4** was now greater than 2.5 h, subsequent reactions were run for 24 h and the effect of varying the number of equivalents of 3-acetoxyaminoquinazolinone **4** in the presence of HMDS was also investigated. Aziridination of carbamate **5** with 2.0 and 4.0 equiv of 3-acetoxyaminoquinazolinone **4** in the presence of 3.0 and 5.0 equiv of HMDS gave aziridine **8** in 55 and 74% conversion, respectively, and in >99:1 dr in each case (Scheme 4).



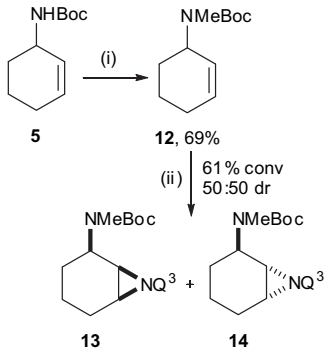
Scheme 4. Reagents and conditions: (i) Q^2NHOAc **4** (2.0 equiv), HMDS (3.0 equiv), CH_2Cl_2, rt, 2.5 h; (ii) Q^2NHOAc **4** (2.0 equiv), HMDS (3.0 equiv), CH_2Cl_2, rt, 24 h; (iii) Q^2NHOAc **4** (4.0 equiv), HMDS (5.0 equiv), CH_2Cl_2, rt, 24 h.

Atkinson et al. have also shown that the C(2)-trifluoromethyl substituted 3-acetoxyaminoquinazolinone **11** (Q^3NHOAc) is far more resistant to decomposition than Q^2NHOAc **4**.[19] Treatment of carbamate **5** with 2.0 equiv of **11** for 24 h gave *syn*-aziridine **10** in 90% conversion as a single diastereoisomer (>99:1 dr). Employing 4.0 equiv of **11** promoted complete conversion to **10**, although further reaction optimisation revealed that treatment of **5** with only 2.0 equiv of **11** over an extended reaction time of 48 h is sufficient to achieve full conversion: following reaction under these conditions **10** was isolated in 93% yield and >99:1 dr. The relative *syn*-configuration within aziridine **10** was assigned on the basis of ^{1}H NMR NOE analysis, which showed strong reciprocal enhancements between the C(1)*H* and C(2)*H* protons, and also by analogy with related substrates (vide infra). In accordance with Atkinson's model **2** for the aziridination of allylic alcohol **1**[9] the high *syn* diastereoselectivity observed upon aziridination of carbamate **5** is consistent with H-bonded delivery of the electrophile on the *syn* face of the neighbouring olefin via a transition state such as **9** (Scheme 5).



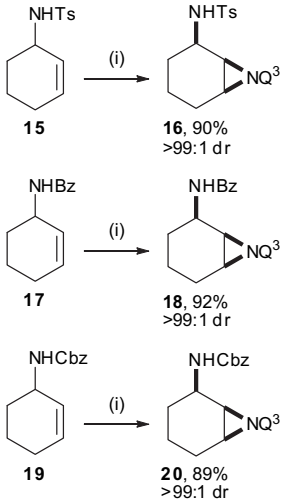
Scheme 5. Reagents and conditions: (i) Q^3NHOAc **11** (2.0 equiv), CH_2Cl_2, rt, 24 h; (ii) Q^3NHOAc **11** (4.0 equiv), CH_2Cl_2, rt, 24 h; (iii) Q^3NHOAc **11** (2.0 equiv), CH_2Cl_2, rt, 48 h.

In order to test this hypothesis, and probe the role of the N*H* proton in the reaction, aziridination of *N*-methyl carbamate **12** was attempted. Carbamate **12** was synthesised in 69% yield by methylation of **5** with NaH and MeI. Subsequent treatment of **12** with 2.0 equiv of **11** for 48 h (i.e., under identical conditions to the reaction of **5**) proceeded to give 61% conversion to an approximately 50:50 ratio of diastereoisomers **13** and **14** (Scheme 6). The poor diastereoselectivity and low reaction conversion observed in this case is consistent with the proposed H-bond directed aziridination of allylic carbamate **5** accelerating the reaction as well as being responsible for the high diastereoselectivity.



Scheme 6. Reagents and conditions: (i) NaH, THF, 0 °C, 30 min then MeI, rt, 24 h; (ii) Q^3NHOAc **11** (2.0 equiv), CH_2Cl_2, rt, 48 h.

The compatibility of this substrate-directed aziridination procedure with various protecting groups was next investigated. Under our optimised conditions, aziridination of sulfonamide **15**, benzamide **17** and benzyl carbamate **19** gave aziridines **16**, **18** and **20** in 90, 92 and 89% yield, respectively, and in >99:1 dr in each case (Scheme 7). The *syn*-relative configuration within benzamide **18** was unambiguously proven by single crystal X-ray analysis (Fig. 1). The relative configurations within **16** and **20** were thus assigned by analogy to that of **18**, and this analysis also supports the assigned *syn*-configurations within **8** and **10**.



Scheme 7. Reagents and conditions: (i) Q^3NHOAc **11** (2.0 equiv), CH_2Cl_2, rt, 48 h.

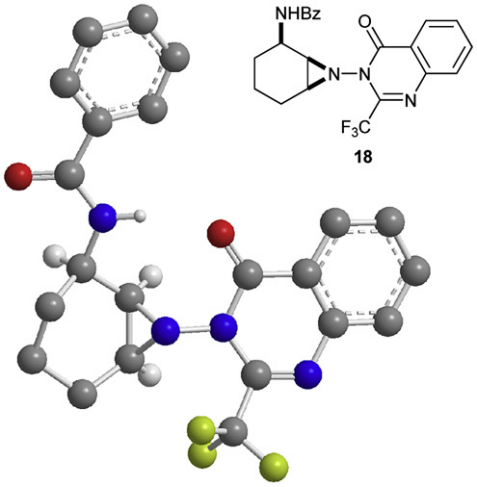
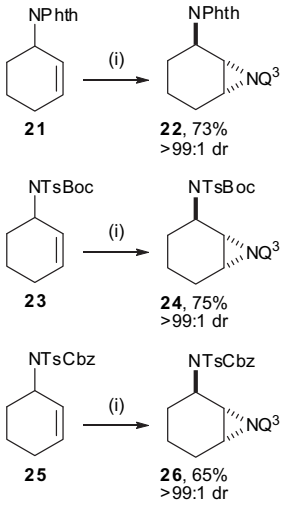


Figure 1. Chem3D representation of the X-ray crystal structure of **18** (some H atoms have been omitted for clarity).

Subsequent studies were directed towards tuning the aziridination protocol to give *anti*-aziridines. It was anticipated that the corresponding *anti*-aziridines may be obtained by removing the H-bonding capacity of the substrate and providing a suitable steric bias to favour *anti* aziridination. As *N*-methyl-*N*-Boc protected carbamate **12** gives aziridines **13** and **14** in approximately 50:50 dr upon treatment with **11**, employing two bulky *N*-protecting groups was expected to favour *anti* aziridination. Three substrates were initially selected: imide **21** and sulfonyl carbamates **23** and **25**. Using the optimised conditions *anti*-aziridines **22**, **24** and **26** were obtained in 73, 75 and 65% yield, respectively, and in >99:1 dr in each case (Scheme 8). The relative configuration within imide **22** was unambiguously proven by single crystal X-ray analysis (Fig. 2); the relative configurations within **24** and **26** were thus assigned by analogy.



Scheme 8. Reagents and conditions: (i) Q^3NHOAc **11** (2.0 equiv), CH_2Cl_2, rt, 48 h.

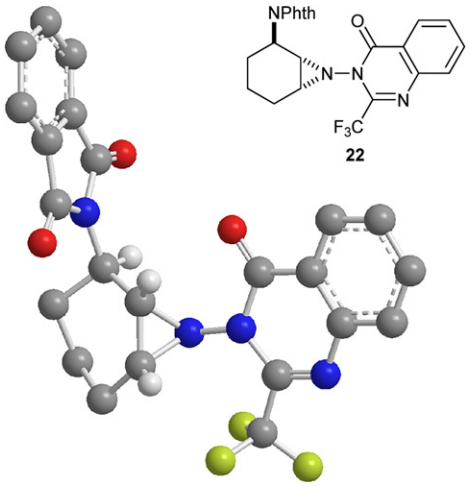


Figure 2. Chem3D representation of the X-ray crystal structure of **22** (some H atoms have been omitted for clarity).

3. Conclusion

In conclusion, a stereodivergent protocol for the aziridination of a range of cyclic allylic amine derivatives with Atkinson's C(2)-trifluoromethyl substituted 3-acetoxyaminoquinazolinone reagent has been developed. N-Protection as a carbamate, amide or sulfonamide leads to highly diastereoselective *syn* aziridination under H-bonded substrate control. Conversely, protection of the nitrogen atom with two bulky protecting groups leads to *anti* aziridination under steric control. In each case the corresponding aziridines are isolated in high yield as single diastereoisomers (>99:1 dr).

4. Experimental

4.1. General experimental

All reactions involving organometallic or other moisture-sensitive reagents were carried out under a nitrogen or argon

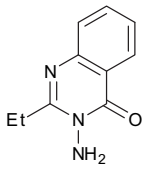
atmosphere using standard vacuum line techniques and glassware that was flame dried and cooled under nitrogen before use. Solvents were dried according to the procedure outlined by Grubbs et al.[20] Water was purified by a Millipore Elix® UV-10 system. All other solvents were used as supplied (analytical or HPLC grade) without prior purification. Organic layers were dried over $MgSO_4$. Thin layer chromatography was performed on aluminium plates coated with 60 F_{254} silica. Plates were visualised using UV light (254 nm), iodine, 1% aq $KMnO_4$, or 10% ethanolic phosphomolybdic acid. Flash column chromatography was performed on Kieselgel 60 silica.

Melting points were recorded on a Gallenkamp Hot Stage apparatus and are uncorrected. Optical rotations were recorded on a Perkin–Elmer 241 polarimeter with a water-jacketed 10 cm cell. Specific rotations are reported in 10^{-1} deg cm^2 g^{-1} and concentrations in grams per 100 mL. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer. Selected characteristic peaks are reported in cm^{-1}. NMR spectra were recorded on Bruker Avance spectrometers in the deuterated solvent stated. The field was locked by external referencing to the relevant deuteron resonance. In cases where methylene protons of carbocyclic ring systems could not be unambiguously assigned to a specific carbon atom, the descriptor 'CH_2' is employed throughout. Low-resolution mass spectra were recorded on either a VG MassLab 20-250 or a Micromass Platform 1 spectrometer. Accurate mass measurements were run on either a Bruker MicroTOF, which was internally calibrated with polyalanine, or a Micromass GCT instrument fitted with a Scientific Glass Instruments BPX5 column (15 m×0.25 mm) using amyl acetate as a lock mass.

4.2. General procedure for aziridination

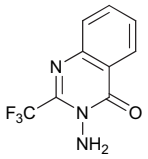
A solution of the requisite aminoquinazolinone (2.0–8.0 equiv) in CH_2Cl_2 was added dropwise over a period of 30 min to a stirred suspension of $PhI(OAc)_2$ (2.0–8.0 equiv) in CH_2Cl_2 at −23 °C. The resultant mixture was stirred for a further 30 min and allowed to warm to rt then a solution of the requisite olefin (1.0 equiv) in CH_2Cl_2 was added dropwise over a period of 10 min. The reaction mixture was then allowed to warm to rt and stirred for 2.5–48 h. After this time, the reaction mixture was diluted with Et_2O, washed sequentially with 0.5 M aq KOH and H_2O, then dried and concentrated in vacuo.

4.2.1. 2-Ethyl-3-aminoquinazolinone.



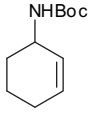
A mixture of methyl 2-aminobenzoate (17.1 mL, 132 mmol) and propionic anhydride (23.7 mL, 185 mmol) was heated without solvent at 105 °C for 30 min, then cooled to 75 °C and diluted with EtOH (50 mL). Hydrazine monohydrate (64.2 mL, 1.32 mol) was added in two portions at 5 min intervals and the resultant mixture was then heated at reflux for 1 h, then allowed to cool to rt and concentrated in vacuo. The residue was dissolved in CH_2Cl_2 and the resultant solution was dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 4:1) gave 2-ethyl-3-aminoquinazolinone as a white crystalline solid (19.2 g, 77%);[21] mp 125–127 °C; {lit.[21] mp 122–123 °C}; δ_H (400 MHz, $CDCl_3$) 1.41 (3H, t, *J* 7.4, CH_3), 3.08 (2H, q, *J* 7.5, CH_2), 4.86 (2H, s, NH_2), 7.43–7.50 (1H, m, *Ar*), 7.66–7.71 (1H, m, *Ar*), 7.72–7.79 (1H, m, *Ar*), 8.25 (1H, d, *J* 7.9, *Ar*).

4.2.2. 2-Trifluoromethyl-3-aminoquinazolin-4-one.



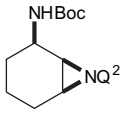
Trifluoroacetic anhydride (60.8 mL, 437 mmol) was added dropwise to a stirred suspension of anthranilic acid (20.0 g, 146 mmol) in $CHCl_3$ (600 mL) and the mixture was then heated at reflux for 1 h. The reaction mixture was then allowed to cool to rt and concentrated in vacuo. Purification via recrystallisation from 60 °C petrol gave 2-trifluoromethyl-benzo[1,3]oxazin-4-one as a white crystalline solid (17.6 g, 56%); mp 48–49 °C; {lit.[19] mp 51–52 °C}; δ_H (200 MHz, $CDCl_3$) 7.71–7.42 (2H, m, *Ar*), 8.00–8.13 (1H, m, *Ar*), 8.19–8.30 (1H, m, *Ar*). 2-Trifluoromethyl-benzo[1,3]oxazin-4-one (12.7 g, 59.0 mmol) was dissolved in EtOH (50 mL) containing hydrazine monohydrate (3.15 mL, 64.9 mmol) and the resultant mixture was stirred for 1 h at rt. The reaction mixture was then concentrated in vacuo and the residue was dissolved in EtOAc (100 mL). The resultant solution was washed with 2 M aq HCl (100 mL) and brine (100 mL), then concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 4:1) to give 2-trifluoromethyl-3-aminoquinazolin-4-one as a white crystalline solid (7.98 g, 59%);[19] mp 146–148 °C; {lit.[19] mp 150–151 °C}; δ_H (400 MHz, $CDCl_3$) 4.92 (2H, s, NH_2), 7.64–7.68 (1H, m, *Ar*), 7.88–7.89 (2H, m, *Ar*), 8.35 (1H, d, *J* 7.7, *Ar*).

4.2.3. tert-Butyl cyclohex-2-en-1-ylcarbamate **5**.



Sodium (2.29 g, 99.6 mmol) was added to a stirred solution of naphthalene (12.8 g, 99.6 mmol) in THF (100 mL) at 0 °C and the resultant mixture was stirred for 30 min at rt. A solution of **23** (7.00 g, 19.9 mmol) in THF (100 mL) was then added to the reaction mixture and the resultant solution was stirred for 2 h at rt. H_2O (100 mL) was then added and the aqueous layer was extracted with Et_2O (3×100 mL). The combined organic extracts were then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 4:1) gave **5** as a white solid (2.00 g, 51%);[12] mp 33–35 °C; {lit.[12] mp 32–34 °C}; δ_H (400 MHz, $CDCl_3$) 1.46 (9H, s, CMe_3), 1.49–1.57 (1H, m, CH_2), 1.58–1.69 (2H, m, CH_2), 1.84–1.94 (1H, m, CH_2), 1.95–2.03 (2H, m, CH_2), 4.15 (1H, br s, C(1)*H*), 4.52 (1H, br s, N*H*), 5.61 (1H, dd, *J* 9.9, 2.6, C(2)*H*), 5.77–5.86 (1H, m, C(3)*H*).

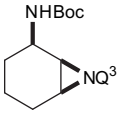
4.2.4. tert-Butyl [(1RS,2RS,6SR)-7-(2′-ethyl-4′-oxoquinazolin-3′-yl)-7-azabicyclo[4.1.0]hept-2-yl]carbamate **8**.



Following the *general procedure*, 2-ethyl-3-aminoquinazolin-4-one (348 mg, 2.00 mmol), $PhI(OAc)_2$ (652 mg, 2.00 mmol) and **5** (50 mg, 0.25 mmol) were reacted in CH_2Cl_2 (10 mL) for 2.5 h at rt to give, after purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 2:1), **8** as a yellow solid (51 mg, 54%, >99:1

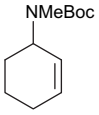
dr); mp 91–93 °C; ν_{max} (KBr) 3390 (N–H), 2944, 1690 (C=O), 1685 (C=O), 1605; δ_H (400 MHz, $CDCl_3$) 1.26–1.33 (1H, m, C(3)H_A), 1.43 (3H, t, *J* 7.4, C(2′)CH_2CH_3), 1.51 (9H, s, CMe_3), 1.56–1.64 (1H, m, C(4)H_A), 1.93–2.14 (4H, m, C(3)H_B, C(4)H_B, C(5)H_2), 2.58 (1H, app t, *J* 7.3, C(6)*H*), 3.04 (2H, q, *J* 7.4, C(2′)CH_2CH_3), 3.08–3.11 (1H, m, C(1)*H*), 3.90–3.94 (1H, m, C(2)*H*), 7.08 (1H, d, *J* 4.8, N*H*), 7.38–7.44 (1H, m, *Ar*), 7.59–7.73 (2H, m, *Ar*), 8.20 (1H, d, *J* 8.1, *Ar*); δ_C (100 MHz, $CDCl_3$) 10.1 (C(2′)CH_2CH_3), 20.0 (*C*(4)), 21.6 (*C*(3)), 26.2 (*C*(5)), 28.1 (C(2′)CH_2CH_3), 28.6 (CMe_3), 47.4 (*C*(2)), 47.6 (*C*(1)), 49.2 (*C*(6)), 79.0 (*C*Me_3), 120.9 (*C*(5′)), 126.3, 126.4, 126.8, 133.8 (*C*(4a′), *C*(7′), *C*(8′), *C*(8a′)), 145.9 (*C*(6′)), 156.0 (*C*(2′)), 157.0 ($CO_2{}^t$Bu), 160.1 (*C*(4′)); *m*/*z* (ESI$^+$) 385 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{21}H_{28}N_4O_3^+$ ([M+H]$^+$) requires 385.2234; found 385.2234.

4.2.5. tert-Butyl [(1RS,2RS,6SR)-7-(2′-trifluoromethyl-4′-oxoquinazolin-3′-yl)-7-azabicyclo[4.1.0]hept-2-yl]carbamate ***10***.



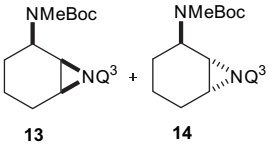
Following the *general procedure*, 2-trifluoromethyl-3-aminoquinazolin-4-one (458 mg, 2.0 mmol), PhI(OAc)$_2$ (644 mg, 2.0 mmol) and carbamate **5** (197 mg, 1.0 mmol) were reacted in CH_2Cl_2 (30 mL) at rt for 48 h to give, after purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 4:1), **10** as a yellow solid (393 mg, 93%, >99:1 dr); mp 114–116 °C; ν_{max} (KBr) 3385 (N–H), 2940, 1695 (C=O), 1690 (C=O), 1605, 1160; δ_H (400 MHz, $CDCl_3$) 1.23–1.36 (2H, m, C(3)H_2), 1.45 (9H, s, CMe_3), 1.57–1.59 (1H, m, C(4)H_A), 1.72–1.77 (1H, m, C(4)H_B), 1.85–1.91 (2H, m, C(5)H_2), 3.81–3.84 (1H, m, C(6)*H*), 3.96–4.01 (1H, m, C(2)*H*), 4.03–4.08 (1H, m, C(1)*H*), 5.46 (1H, d, *J* 7.6, N*H*), 7.57–7.61 (1H, m, *Ar*), 7.81–7.82 (2H, m, *Ar*), 8.21 (1H, d, *J* 8.1, *Ar*); δ_H (500 MHz, C_6D_6) 0.69–0.82 (1H, m, C(4)H_A), 1.10–1.20 (1H, m, C(4)H_B), 1.21–1.37 (3H, m, C(3)H_A, C(5)H_2), 1.47 (9H, s, CMe_3), 1.61 (1H, d, *J* 11.8, C(3)H_B), 3.19 (1H, t, *J* 6.7, C(6)*H*), 3.89 (1H, dd, *J* 7.2, 4.0, C(1)*H*), 5.81 (1H, d, *J* 7.4, N*H*), 6.91 (1H, t, *J* 7.5, *Ar*), 7.09 (1H, q, *J* 7.7, *Ar*), 7.48 (1H, d, *J* 8.0, *Ar*), 7.96–8.05 (1H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 19.8 (*C*(4)), 21.8 (*C*(5)), 26.7 (*C*(3)), 28.4 (C*Me*$_3$), 41.4 (*C*(1)), 42.0 (*C*(6)), 46.3 (*C*(2)), 79.3 (*C*Me_3), 123.0 (*C*(5′)), 126.6, 128.4, 129.2, 134.8 (*C*(4a′), *C*(7′), *C*(8′), *C*(8a′)), 143.9 (*C*(6′)), 155.4 ($CO_2{}^t$Bu), 160.7 (*C*(4′));[22] *m*/*z* (ESI$^+$) 425 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{20}H_{23}F_3N_4O_3^+$ ([M+H]$^+$) requires 425.1795; found 425.1803.

4.2.6. tert-Butyl N-methyl-N-(cyclohex-2-en-1-yl)carbamate ***12***.



A solution of carbamate **5** (197 mg, 1.00 mmol) in THF (5 mL) was added dropwise to a stirred suspension of NaH (60% dispersion in mineral oil, 80 mg, 2.00 mmol) in THF (5 mL) at 0 °C. After 30 min, MeI (0.16 mL, 2.50 mmol) was added and the resultant mixture was stirred at rt for 16 h. MeOH (1 mL) was then added, followed by H_2O (1 mL) and satd aq NH_4Cl (10 mL). The aqueous layer was extracted with Et_2O (3×20 mL) and the combined organic extracts were washed with brine (20 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 49:1) gave **12** as a colourless oil (146 mg, 69%); ν_{max} (film) 2930, 1694 (C=O), 1445, 1396, 1315, 1255, 1150, 935, 885, 860, 775, 645; δ_H (400 MHz, $CDCl_3$) 1.46 (9H, s, CMe_3), 1.62–1.65 (1H, m, C(5)H_A), 1.77–1.82 (2H, m, C(4)H_2), 1.97–1.99 (2H, m, C(5)H_B, C(6)H_A), 2.69–2.81 (4H, m, C(6)H_B, N*Me*), 4.76 (1H, br s, C(1)*H*), 5.45 (1H, app d, *J* 9.9, C(2)*H*), 5.84–5.86 (1H, m, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 21.4 (*C*(5)), 24.6 (*C*(4)), 28.5 (C*Me*$_3$), 28.9 (*C*(6)), 29.1 (N*Me*), 36.8 (*C*(1)), 79.3 (*C*Me_3), 90.1 (*C*(2)), 99.1 (*C*(3)), 128.9 (C=O); *m*/*z* (ESI$^+$) 234 ([M+Na]$^+$, 80%); HRMS (ESI$^+$) $C_{12}H_{21}NNaO_2^+$ ([M+Na]$^+$) requires 234.1465; found 234.1464.

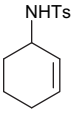
4.2.7. tert-Butyl (1RS,2RS,6SR)- and (1SR,2RS,6RS)-N-methyl-N-[7-(2′-trifluoromethyl-4′-oxoquinazolin-3′-yl)-7-azabicyclo[4.1.0]hept-2-yl]carbamate ***13*** *and* ***14***.



Following the *general procedure*, 2-trifluoromethyl-3-aminoquinazolin-4-one (108 mg, 0.472 mmol), PhI(OAc)$_2$ (152 mg, 0.472 mmol) and **12** (50 mg, 0.236 mmol) were reacted in CH_2Cl_2 (30 mL) at rt for 48 h to give a 38:31:31 mixture of **12**/**13**/**14**.

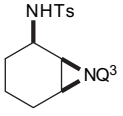
Data for **13** and **14**: δ_H (400 MHz, $CDCl_3$) [selected peaks] 2.69 (3H, br s, N*Me*), 2.74 (3H, br s, N*Me*), 3.80 (2H, br s, C(1)*H*, C(2)*H*), 3.90 (2H, br s, C(1)*H*, C(2)*H*).

4.2.8. N-Cyclohex-2-en-1-yl-toluenesulfonamide ***15***.



TFA (2.64 mL, 35.6 mmol) was added to a stirred solution of **23** (2.50 g, 7.11 mmol) in CH_2Cl_2 (50 mL) and the resultant mixture was stirred for 1 h at rt, then concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 2:1) gave **15** as a white crystalline solid (840 mg, 47%);[12] mp 83–85 °C; {lit.[12] mp 82–84 °C}; δ_H (400 MHz, $CDCl_3$) 1.49–1.67 (3H, m, CH_2), 1.69–1.83 (1H, m, CH_2), 1.94 (2H, br s, CH_2), 2.44 (3H, s, C(4′)*Me*), 3.82 (1H, br s, C(1)*H*), 4.43 (1H, d, *J* 7.7, N*H*), 5.35 (1H, d, *J* 9.6, C(2)*H*), 5.77 (1H, d, *J* 9.7, C(3)*H*), 7.31 (2H, d, *J* 7.7, C(3′)*H*, C(5′)*H*), 7.78 (2H, d, *J* 7.7, C(2′)*H*, C(6′)*H*).

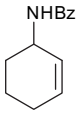
4.2.9. N-[(1RS,2SR,6RS)-7-(2′-Trifluoromethyl-4′-oxoquinazolin-3′-yl)-7-azabicyclo[4.1.0]-hept-2-yl]-toluenesulfonamide ***16***.



Following the *general procedure*, 2-trifluoromethyl-3-aminoquinazolin-4-one (183 mg, 0.801 mmol), PhI(OAc)$_2$ (258 mg, 0.801 mmol) and sulfonamide **15** (100 mg, 0.400 mmol) were reacted in CH_2Cl_2 (10 mL) at rt for 48 h to give, after purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 13:7), **16** as a yellow solid (169 mg, 85%, >99:1 dr); mp 49–51 °C; ν_{max} (KBr) 3360 (N–H), 2950, 1685 (C=O), 1605, 1330 (S–N), 1160 (S=O); δ_H (400 MHz, $CDCl_3$) 1.20–1.26 (1H, m, C(4)H_A), 1.40–1.46 (1H, m, C(3)H_A), 1.48–1.53 (1H, m, C(4)H_B), 1.62–1.68 (1H, m, C(3)H_B), 1.79–1.85 (2H, m, C(5)H_2), 1.96 (3H, s, C(4″)*Me*), 3.70–3.75 (1H, m, C(6)*H*), 3.75–3.80 (2H, m, C(1)*H*, C(2)*H*), 5.68 (1H, d, *J* 7.3, N*H*), 7.01 (2H, d, *J* 8.1, C(3″)*H*, C(5″)*H*), 7.56–7.66 (1H, m, *Ar*), 7.76 (2H, d, *J* 8.1, C(2″)*H*, C(6″)*H*), 7.82–7.87 (2H, m, *Ar*), 8.14 (1H, d, *J* 7.8, *Ar*); δ_C (100 MHz, $CDCl_3$) 19.1 (*C*(4)), 21.0 (C(4″)*Me*), 21.6 (*C*(5)), 27.7 (*C*(3)), 40.3 (*C*(1)), 42.0 (*C*(6)), 49.0 (*C*(2)), 123.0 (*C*(5′)), 126.5 (*Ar*), 126.7 (*C*(2″), *C*(6″)), 128.6 (*Ar*), 129.4 (*Ar*), 129.4 (*C*(3″), *C*(5″)), 135.0 (*Ar*), 138.6 (*C*(1″)), 143.1 (*C*(4″)), 143.7 (*C*(2′)), 160.4 (*C*(4′));[22] *m*/*z* (ESI$^+$)

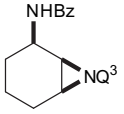
479 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{22}H_{22}F_3N_4O_3S^+$ ([M+H]$^+$) requires 479.1359; found 479.1357.

*4.2.10. (RS)-N-(Cyclohex-2-en-1-yl)benzamide **17**.*



A solution of **1** (980 mg, 10.0 mmol) in THF (5 mL) was added to a mixture of $Bi(OTf)_3$ (328 mg, 0.500 mmol), KPF_6 (92 mg, 0.500 mmol), benzamide (1.82 g, 15.0 mmol) and $MgSO_4$ (~1.5 g) in THF (50 mL). The resultant mixture was stirred at rt for 16 h then filtered through Celite (eluent Et_2O). The filtrate was then concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 1:0 to 9:1 gradient elution) gave **17** as a white solid (570 mg, 28%);[23] mp 96–98 °C; {lit.[23] mp 102–104 °C}; ν_{max} (KBr) 3300 (N–H), 2935 (C–H), 1635 (C=O), 1535, 1490, 1330, 1080, 695, 665; δ_H (400 MHz, $CDCl_3$) 1.57–1.72 (3H, m, CH_2), 1.93–2.02 (3H, m, CH_2), 4.64–4.70 (1H, m, C(1)H), 5.62–5.68 (1H, m, C(2)H), 5.85–5.90 (1H, m, C(3)H), 6.34 (1H, d, *J* 7.5, NH), 7.36–7.40 (2H, m, Ph), 7.44–7.48 (2H, m, Ph), 7.75–7.78 (2H, m, Ph).

*4.2.11. N-[(1RS,2RS,6SR)-7-(2′-Trifluoromethyl-4′-oxoquinazolin-3′-yl)-7-azabicyclo[4.1.0]hept-2-yl]benzamide **18**.*



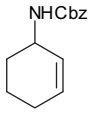
Following the *general procedure*, 2-trifluoromethyl-3-aminoquinazolin-4-one (229 mg, 1.00 mmol), $PhI(OAc)_2$ (322 mg, 1.00 mmol) and amide **17** (101 mg, 0.500 mmol) were reacted in CH_2Cl_2 (15 mL) at rt for 48 h to give, after purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 1:1), **18** as a white solid (197 mg, 92%, >99:1 dr); mp 136–138 °C; ν_{max} (KBr) 3370 (N–H), 2940, 1685 (C=O), 1655 (amide I), 1605, 1530 (amide II); δ_H (400 MHz, $CDCl_3$) 1.27–1.45 (2H, m, C(3)H_A, C(4)H_A), 1.56–1.70 (1H, m, C(4)H_B), 1.92–2.14 (3H, m, C(3)H_B, C(5)H_2), 3.40–3.51 (1H, m, C(6)*H*), 3.58 (1H, dd, *J* 7.8, 3.4, C(1)*H*), 4.45 (1H, d, *J* 3.3, C(2)*H*), 7.39–7.53 (3H, m, *Ar*), 7.55–7.65 (1H, m, *Ar*), 7.76–7.86 (2H, m, *Ar*), 7.98 (2H, d, *J* 8.0, *Ar*), 8.16–8.30 (2H, m, *Ar*, N*H*); δ_C (100 MHz, $CDCl_3$); 15.3 (*C*(4)), 19.8 (*C*(5)), 26.1 (*C*(3)), 44.6 (*C*(1)), 46.4 (*C*(2)), 46.9 (*C*(6)), 122.5 (*C*(5′)), 126.7 (*Ar*), 127.1 (*o*,*m*-*Ph*), 128.4 (*Ar*), 128.5 (*o*,*m*-*Ph*), 129.4 (*Ar*), 131.3 (*p*-*Ph*), 134.4 (*i*-*Ph*), 134.9 (*Ar*), 143.6 (*C*(6′)), 160.3 (*C*(4′)), 166.6 (PhCONH);[22] *m*/*z* (ESI$^+$) 429 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{22}H_{19}F_3N_4O_2^+$ ([M+H]$^+$) requires 429.1533; found 429.1529.

*4.2.11.1. X-ray crystal structure determination for **18**.* Data were collected using an Enraf-Nonius κ-CCD diffractometer with graphite monochromated Mo Kα radiation using standard procedures at 190 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[24]

X-ray crystal structure data for **18** [$C_{29.33}H_{25.33}F_4N_{5.33}O_{2.67}$]: *M*=428.41, monoclinic, space group *C* 2/*c*, *a*=42.5409(11) Å, *b*=6.8163 (2) Å, *c*=13.8366(5) Å, *β*=101.7744(9)°, *V*=3927.8(2) Å^3, *Z*=6, *μ*=0.155 mm^{-1}, colourless plate, crystal dimensions=0.1×0.2×0.3 mm^3. A total of 4338 unique reflections were measured for 5<*θ*<27 and 2417 reflections were used in the refinement. The final parameters were wR_2=0.040 and R_1=0.035 [$I>3.0\sigma(I)$].

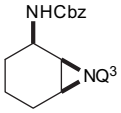
Crystallographic data (excluding structure factors) has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 772458. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

*4.2.12. Benzyl (RS)-cyclohex-2-en-1-ylcarbamate **19**.*



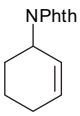
A solution of **1** (980 mg, 10.0 mmol) in THF (5 mL) was added to a mixture of $Bi(OTf)_3$ (328 mg, 0.500 mmol), KPF_6 (92 mg, 0.500 mmol), benzyl carbamate (2.27 g, 15.0 mmol) and $MgSO_4$ (~1.5 g) in THF (50 mL). The resultant mixture was stirred at rt for 16 h then filtered through Celite (eluent Et_2O). The filtrate was then concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 1:0 to 9:1 gradient elution) gave **19** as a white solid (1.92 g, 83%);[25] mp 65–67 °C; δ_H (400 MHz, $CDCl_3$) 1.01–1.93 (3H, m, CH_2), 1.45–1.64 (3H, m, CH_2), 4.22 (1H, br s, C(1)H), 5.02–5.09 (2H, m, OCH_2Ph), 5.39 (1H, br s, NH), 5.58 (1H, d, *J* 9.9, C(2)H), 5.74–5.79 (1H, m, C(3)H), 7.23–7.29 (5H, m, Ph).

*4.2.13. Benzyl [(1RS,2RS,6SR)-7-(2′-trifluoromethyl-4′-oxaquinazolin-3′-yl)-7-azabicyclo[4.1.0]hept-2-yl]carbamate **20**.*



Following the *general procedure*, 2-trifluoromethyl-3-aminoquinazolin-4-one (458 mg, 2.0 mmol), $PhI(OAc)_2$ (644 mg, 2.0 mmol) and carbamate **19** (231 mg, 1.0 mmol) were reacted in CH_2Cl_2 (30 mL) at rt for 48 h to give, after purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 13:7), **20** as a yellow solid (406 mg, 89%, >99:1 dr); mp 44–47 °C; ν_{max} (KBr) 3365 (N–H), 2945, 1695 (C=O), 1690 (C=O), 1605; δ_H (400 MHz, $CDCl_3$) 1.24–1.39 (2H, m, C(3)H_A, C(4)H_A), 1.56–1.62 (1H, m, C(4)H_B), 1.78–1.84 (1H, m, C(3)H_B), 1.87–1.97 (2H, m, C(5)H_2), 3.74–3.77 (1H, m, C(6)*H*), 3.97–4.02 (1H, m, C(1)*H*), 4.03–4.09 (1H, m, C(2)*H*), 5.09–5.15 (2H, m, CH_2Ph), 5.91 (1H, d, *J* 7.6, N*H*), 7.25–7.38 (5H, m, *Ph*), 7.56–7.60 (1H, m, *Ar*), 7.78–7.81 (2H, m, *Ar*), 8.20 (1H, d, *J* 7.8, *Ar*); δ_C (100 MHz, $CDCl_3$) 19.8 (*C*(4)), 21.7 (*C*(5)), 26.6 (*C*(3)), 41.8 (*C*(1)), 43.0 (*C*(6)), 47.0 (*C*(2)), 66.6 (CH_2Ph), 126.6, 128.4, 128.7, 129.3, 134.8 (*C*(4a′), *C*(5′), *C*(7′), *C*(8′), *C*(8a′)), 128.0 (*p*-*Ph*), 128.1, 128.4 (*o*, *m*-*Ph*), 136.7 (*i*-*Ph*), 143.8 (*C*(6′)), 156.0 (CO_2Bn), 160.6 (*C*(4′));[22] *m*/*z* (ESI$^+$) 459 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{23}H_{21}F_3N_4O_3^+$ ([M+H]$^+$) requires 459.1639; found 459.1641.

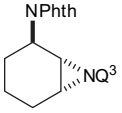
*4.2.14. N-(Cyclohex-2-en-1-yl)phthalimide **21**.*



Phthalimide (3.00 g, 20.4 mmol), PPh_3 (5.35 g, 20.4 mmol) and DEAD (3.21 mL, 20.4 mmol) were added to a stirred solution of **1** (1.00 g, 10.2 mmol) in THF (75 mL) at rt. The resultant solution was stirred at rt for 24 h then concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 9:1) gave **21** as a white crystalline solid (1.21 g, 52%);[26] mp 109–111 °C {lit.[26] mp 113–114 °C}; δ_H (400 MHz, $CDCl_3$) 1.70–1.78 (2H, m, CH_2), 1.89–1.97 (2H, m, CH_2), 2.06–2.23 (2H, m, CH_2), 4.87–4.93 (1H, m, C

(1)*H*), 5.56 (1H, app d, *J* 10.2, C(2)*H*), 5.93–5.96 (1H, m, C(3)*H*), 7.69–7.72 (2H, m, C(3′)*H*, C(4′)*H*), 7.82–7.84 (2H, m, C(2′)*H*, C(5′)*H*).

4.2.15. N-[(1SR,2RS,6RS)-7-(2′-Trifluoromethyl-4′-oxoquinazolin-3′-yl)-7-azabicyclo[4.1.0]hept-2-yl]phthalimide ***22****.*



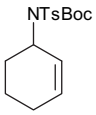
Following the *general procedure*, 2-trifluoromethyl-3-aminoquinazolin-4-one (458 mg, 2.00 mmol), $PhI(OAc)_2$ (644 mg, 2.00 mmol) and imide **21** (227 mg, 1.00 mmol) were reacted in CH_2Cl_2 (30 mL) at rt for 48 h to give, after purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 3:1), **22** as a white crystalline solid (330 mg, 73%, >99:1 dr); mp 212–214 °C; ν_{max} (KBr) 2945, 1770 (imide), 1710 (imide), 1705 (C=O), 1605; δ_H (400 MHz, $CDCl_3$) 1.52–1.62 (2H, m, C(4)H_2), 1.71–1.77 (2H, m, C(3)H_2), 183–1.88 (1H, m, C(5)H_A), 2.28–2.32 (1H, app d, *J* 14.2, C(5)H_B), 3.76–3.80 (1H, m, C(6)*H*), 3.92–3.97 (2H, m, C(1)*H*, C(2)*H*), 7.52–7.56 (1H, m, *Ar*), 7.71–7.74 (2H, m, C(3″)*H*, C(4″)*H*), 7.77–7.79 (2H, m, *Ar*), 7.83–7.85 (2H, m, C(2″)*H*, C(5″)*H*), 8.14 (1H, d, *J* 7.8, *Ar*); δ_C (100 MHz, $CDCl_3$) 17.1 (*C*(4)), 22.5 (*C*(5)), 25.9 (*C*(3)), 41.6, 42.9 (*C*(1), *C*(6)), 45.7 (*C*(2)), 122.9 (*Ar*), 123.3 (*C*(2″), *C*(5″)), 126.4, 128.4, 128.7, 129.1 (*Ar*), 131.9 (*C*(1″), *C*(6″)), 134.0 (*C*(3″), *C*(4″)), 134.6 (*Ar*), 143.9 (*C*(6′)), 160.6 (*C*(4′)), 167.7 (N(C=O)$_2$);[22] *m*/*z* (ESI$^+$) 455 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{23}H_{17}F_3N_4O_3^+$ ([M+H]$^+$) requires 455.1326; found 455.1329.

4.2.15.1. X-ray crystal structure determination for ***22****.* Data were collected using an Enraf-Nonius κ-CCD diffractometer with graphite monochromated Mo Kα radiation using standard procedures at 190 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[24]

X-ray crystal structure data for **22** [$C_{30.67}H_{22.67}F_4N_{5.33}O_4$]: *M*=454.41, monoclinic, space group *C* 2/*c*, *a*=21.6579(3) Å, *b*=16.3647 (3) Å, *c*=14.6212(3) Å, *β*=127.1892(7)°, *V*=4128.30(13) Å^3, *Z*=6, *μ*=0.117 mm^{-1}, colourless plate, crystal dimensions= 0.2×0.2×0.3 mm^3. A total of 4683 unique reflections were measured for 5<*θ*<27 and 2833 reflections were used in the refinement. The final parameters were *wR*$_2$=0.050 and *R*$_1$=0.041 [*I*>3.0*σ*(*I*)].

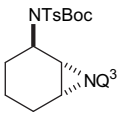
Crystallographic data (excluding structure factors) has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 772459. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

4.2.16. tert-Butyl N-tosyl-(cyclohex-2-en-1-yl)carbamate ***23****.*



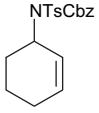
PPh_3 (32.2 g, 123 mmol), **1** (6.03 g, 61.4 mmol) and DEAD (14.5 mL, 92.1 mmol) were added to a stirred solution of TsNHBoc (25.0 g, 92.1 mmol) in THF (125 mL). The resulting mixture was stirred at rt for 24 h then concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 9:1) gave **23** as a white solid (18.8 g, 87%);[12] mp 83–85 °C; {lit.[12] mp 84–86 °C}; δ_H (400 MHz, $CDCl_3$) 1.35 (9H, s, C*Me*$_3$), 1.66–1.80 (1H, m, C*H*$_2$), 1.85–1.96 (1H, m, C*H*$_2$), 1.97–2.12 (3H, m, C*H*$_2$), 2.15–2.29 (1H, m, C*H*$_2$), 2.45 (2H, s, C(4′)*Me*), 5.05–5.16 (1H, m, C(1)*H*), 5.52 (1H, d, *J* 10.2, C(2)*H*), 5.70–5.79 (1H, m, C(3)*H*), 7.31 (2H, d, *J* 8.0, C(3′)*H*, C(5′)*H*), 7.82 (2H, d, *J* 8.4, C(2′)*H*, C(6′)*H*).

4.2.17. tert-Butyl N-tosyl-[(1RS,2RS,6RS)-7-(2′-trifluoromethyl-4′-oxoquinazolin-3′-yl)-7-azabicyclo[4.1.0]hept-2-yl]carbamate ***24****.*



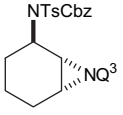
Following the *general procedure*, 2-trifluoromethyl-3-aminoquinazolin-4-one (458 mg, 2.00 mmol), $PhI(OAc)_2$ (644 mg, 2.00 mmol) and **23** (352 mg, 1.00 mmol) were reacted in CH_2Cl_2 (30 mL) at rt for 48 h to give, after purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 3:1), **24** as a white crystalline solid (434 mg, 75%, >99:1 dr); mp 138–140 °C; ν_{max} (KBr) 2950, 1690 (C=O), 1680 (C=O), 1605, 1340 (S–N), 1165 (S=O); δ_H (400 MHz, $CDCl_3$) 1.41 (9H, s, C*Me*$_3$), 1.53–1.58 (2H, m, C(5)H_2), 1.68–1.86 (3H, m, C(3)H_2, C(4)H_A), 2.18–2.23 (1H, m, C(4)H_B), 2.33 (3H, s, C(4″)*Me*), 3.88–3.94 (2H, m, C(1)*H*, C(6)*H*), 4.88 (1H, dd, *J* 6.7, 11.5, C(2)*H*), 7.24 (2H, d, *J* 8.1, C(3″)*H*, C(5″)*H*), 7.58–7.65 (1H, m, *Ar*), 7.82–7.83 (2H, m, *Ar*), 7.90 (2H, d, *J* 8.1, C(2″)*H*, C(6″)*H*), 8.20 (1H, d, *J* 8.1, *Ar*); δ_C (100 MHz, $CDCl_3$) 15.2 (*C*(5)), 21.5 (C(4″)*Me*), 22.5 (*C*(4)), 27.0 (*C*(6)), 28.0 (C*Me*$_3$), 41.7, 44.2 (*C*(1), *C*(3)), 53.6 (*C*(2)), 84.6 (*C*Me$_3$), 123.0 (*C*(5′)), 126.5 (*Ar*), 128.1 (*C*(2″), *C*(6″)), 128.5 (*Ar*), 129.1 (*Ar*), 129.2 (*C*(3″), *C*(5″)), 134.7 (*Ar*), 137.4 (*C*(1″)), 144.0, 144.1 (*C*(6′), *C*(2′)), 150.6 (*C*O$_2$^{t}Bu), 160.8 (*C*(4′));[22] *m*/*z* (ESI$^+$) 579 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{27}H_{29}F_3N_4O_5S^+$ ([M+H]$^+$) requires 579.1884; found 579.1883.

4.2.18. Benzyl N-tosyl-(cyclohex-2-en-1-yl)carbamate ***25****.*



PPh_3 (2.67 g, 10.2 mmol), **1** (500 mg, 5.09 mmol) and DEAD (1.20 mL, 7.64 mmol) were added to a stirred solution of TsNHCbz (2.33 g, 7.64 mmol) in THF (20 mL). The resulting mixture was stirred at rt for 24 h then concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 9:1) gave **25** as a white solid (1.35 g, 69%); mp 68–70 °C; ν_{max} (KBr) 2940, 2360, 1731 (C=O), 1597, 1469, 1455, 1355, 1257, 1170, 1090; δ_H (400 MHz, $CDCl_3$) 1.65–1.77 (1H, m, C(5)H_A), 1.85–1.90 (1H, m, C(5)H_B), 1.96–2.05 (3H, m, C(4)H_2, C(6)H_A), 2.16–2.26 (1H, m, C(6)H_B), 2.41 (3H, s, C(4′)*Me*), 5.07 (2H, s, OCH_2Ph), 5.16–5.22 (1H, m, C(1)*H*), 5.51 (1H, app d, *J* 10.4, C(2)*H*), 5.73–5.76 (1H, m, C(3)*H*), 7.10–7.23 (5H, m, *Ph*), 7.32–7.34 (2H, m, C(3′)*H*, C(5′)*H*), 7.73 (2H, d, *J* 8.3, C(2′)*H*, C(6′)*H*); δ_C (100 MHz, $CDCl_3$) 21.6 (C(4′)*Me*), 22.5 (*C*(5)), 23.9 (*C*(4)), 28.2 (*C*(6)), 56.7 (*C*(1)), 68.7 (OCH_2Ph), 127.8, 128.1, 128.4, 128.5, 128.9, 129.3 (*o*,*m*,*p*-*Ph*, *C*(2′), *C*(3′), *C*(4′), *C*(5′), *C*(6′),), 133.6 (*i*-*Ph*), 134.5 (*C*(2)), 137.2 (*C*(3)), 144.2 (*C*(1′)), 151.9 (C=O); *m*/*z* (ESI$^+$) 408 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{21}H_{23}NNaO_4S^+$ ([M+H]$^+$) requires 408.1240; found 408.1239.

4.2.19. Benzyl N-tosyl-[(1RS,2RS,6RS)-7-(2′-trifluoromethyl-4′-oxoquinazolin-3′-yl)-7-azabicyclo[4.1.0]hept-2-yl]carbamate ***26****.*



Following the *general procedure*, 2-trifluoromethyl-3-aminoquinazolin-4-one (458 mg, 2.00 mmol), $PhI(OAc)_2$ (644 mg,

2.00 mmol) and **25** (386 mg, 1.00 mmol) were reacted in CH_2Cl_2 (30 mL) at rt for 48 h to give, after purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 3:1), **26** as a white crystalline solid (398 mg, 65%, >99:1 dr); mp 124–126 °C; ν_{max} (KBr) 2940, 1690 (C=O), 1685 (C=O), 1605, 1345 (S–N), 1160 (S=O); δ_H (400 MHz, $CDCl_3$) 1.35–1.57 (3H, m, C(3)H_A, C(4)H_2), 1.63–1.78 (1H, m, C(5)H_A), 1.80–1.92 (1H, m, C(5)H_B), 2.10 (1H, d, *J* 11.8, C(3)H_B), 2.32 (3H, s, *Me*), 3.77 (1H, d, *J* 7.5, C(2)*H*), 3.87 (1H, d, *J* 7.5, C(1)*H*), 4.96 (1H, dd, *J* 11.4, 6.9, C(6)*H*), 5.11 (2H, s, CH_2Ph), 7.15 (2H, d, *J* 8.0, *Ar*), 7.27 (2H, d, *J* 1.9, *Ph*), 7.35 (3H, d, *J* 2.3, *Ph*), 7.56–7.65 (1H, m, *Ar*), 7.78–7.88 (4H, m, *Ar*), 8.21 (1H, d, *J* 8.0, *Ar*); δ_C (100 MHz, $CDCl_3$) 17.1 (*C*(4)), 21.5 (C(4″)*Me*), 22.2 (*C*(3)), 26.9 (*C*(5)), 42.0 (*C*(2)), 44.1 (*C*(1)), 53.8 (*C*(6)), 69.3 (CH_2Ph), 123.0 (*C*(5′)), 126.4 (*Ar*), 12.85, 128.6, 128.8, 129.3 (*C*(2″), *C*(3″), *C*(5″), *C*(6″), *o*,*m*-*Ph*), 128.5, 128.8, 129.2 (*p*-*Ph*, *Ar*), 134.2, 136.7 (*C*(1″), *i*-*Ph*), 134.7 (*Ar*), 144.0 (*C*(6′)), 144.5 (*C*(4″)), 151.8 (*C*$O_2$$CH_2$Ph), 160.6 (*C*(4′));[22] *m*/*z* (ESI$^+$) 613 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{30}H_{27}F_3N_4O_5S^+$ ([M+H]$^+$) requires 613.1727; found 613.1727.

Acknowledgements

The authors would like to the Oxford Chemical Crystallography Service for the use of their x-ray diffractometers.

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